DISSERTATION ON

A STUDY ON BODE INDEX AS A PREDICTOR OF SEVERITY AND SYSTEMIC INVOLVEMENT IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Submitted in partial fulfillment of the requirements for

M.D.DEGREE BRANCH -1 GENERAL MEDICINE

of

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERISTY,

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

MARCH – 2009.

CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON BODE INDEX AS A PREDICTOR OF SEVERITY AND SYSTEMIC INVOLVEMENT IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" submitted by **Dr. SOJAN GEORGE K.** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2009 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation entitled "**A STUDY ON BODE INDEX AS A PREDICTOR OF SEVERITY AND SYSTEMIC INVOLVEMENT IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" is done by me at t he madras medical college and Government General Hospital, Chennai during 2007-2008 under the guidance and supervision of Prof .D. Rajasekaran, M.D.

This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of M.D. DEGREE IN GENERAL MEDICINE (BRANCH–I).

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ACKNOWLEDGEMENT

I would like to express my sincere gratitude to **Prof. T. P. KALANITI, M.D.**, The Dean, Madras Medical College, for having permitted me to use the hospital material in this study.

I am immensely grateful to **Prof. C. Rajendran, M.D.,** Director, Institute of Internal Medicine, for his suggestions and encouragement.

I am greatly indebted to my beloved unit chief and teacher **Prof. D. Rajasekaran, M.D.,** Additional professor, Institute of Internal Medicine, who encouraged, helped and guided me throughout this study.

I express my sincere thanks to my unit Assistant Professors, **Dr. G. Subburagavalu, M.D., Dr. A. Aravind, M.D., Dr. S. Tito, M.D.** for their thoughtful guidance throughout the work.

I thank all the professors, assistant professors and post graduates of the department of biochemistry for their valuable support in the biochemical analysis.

I thank all my colleagues and friends for their constant encouragement and valuable criticism.

I express my gratitude for the generosity shown by all the patients who participated in the study. If at all this study contributes a little to relieve their suffering, I feel that I have repaid a part of my debt.

I am extremely thankful to my family members for their continuous support. Above all I thank my God Almighty for His immense blessings.

CONTENTS

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population. It is projected to rank fifth in 2020 in burden of disease caused worldwide, according to a study published by the World Bank/World Health Organization[1]. The disease causes a heavy burden on the global health care resources. The costs involved in the treatment and evaluation is directly proportional to the pulmonary and the extra pulmonary components of the disease[2].

'Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases' [3].

The pathogenesis and clinical manifestations of COPD are not restricted to pulmonary inflammation and structural remodeling. Rather, this

disorder is associated with clinically significant systemic alterations in biochemistry and organ function. The systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute-phase proteins. As in other chronic inflammatory conditions, weight loss, muscle wasting, hypo proteinemia and tissue depletion are commonly seen in COPD patients[4]. Selective wasting of fat-free mass coupled with impaired respiratory and peripheral muscle function and a reduced capacity for exercise occur in COPD patients. Indeed, weight loss may directly impact poor prognosis in COPD patients.

The severity of COPD is usually assessed on the basis of a single parameter – forced expiratory volume in one second (FEV1). However the patients with COPD have systemic manifestations that are not reflected by the FEV_1. Hence a multidimensional grading system that assessed the respiratory and systemic expressions of COPD was designed to predict outcome in these patients[5]. The four factors that predicted the severity most were the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the six-minute–walk test. These variables were used to construct the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death.

The process of allocating scarce medical resources to the most needed patients can be extremely difficult in diseases which affect a large number of patients. Decision makers need a rational and consistent scoring system that is designed to identify those who are maximally in need of a diagnostic or a therapeutic intervention under a health-care budget constraint. BODE index has been proposed to serve this purpose in patients with chronic obstructive pulmonary disease (COPD)[6].

In our study we analyzed the BODE index as a predictor of hospitalization and severity of systemic involvement.

AIMS AND OBJECTIVES

1. To determine whether higher BODE index in chronic obstructive pulmonary disease correlates with more years of cigarette smoking.
2. To determine whether higher BODE index is associated with more days of hospitalisation.
3. To determine whether higher BODE index is associated with more severe cardiac involvement.
4. To determine whether higher BODE index correlates with poor nutritional status.
5. To determine the correlation between BODE index and the level of systemic inflammation in patients with COPD.

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. COPD is one of the leading causes of morbidity and mortality worldwide and imparts a substantial economic burden on individuals and society.

DEFINITION

Chronic obstructive pulmonary disease (COPD) was initially defined as 'a disease state characterized by chronic airflow limitation due to chronic bronchitis and emphysema'. Chronic bronchitis has been defined in clinical terms as 'the presence of chronic productive cough for at least 3 consecutive months in 2 consecutive years. Other causes of chronic productive cough must be ruled out'. Emphysema, on the other hand, has been defined by its pathologic description: 'an abnormal enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their walls and without obvious fibrosis'.

However the definition of COPD has undergone major revision. The new GOLD guidelines[3] and the ATS/ERS definition[7] reflect these scientific

advances: “Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases” [3]. While the new guidelines do not specifically include chronic bronchitis and emphysema in the definition of COPD, it is made clear that they are considered the predominant causes of COPD. The airflow limitation is caused by mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) the relative contribution of each varies from person to person[3].

EPIDEMIOLOGY

Using the World Health Organization/World Bank Global Burden of Disease Study data, the worldwide prevalence of COPD in 1990 was estimated at 9.34/1000 in men and 7.33/1000 in women[8,9]. This was an underestimation of true prevalence of COPD since the estimates included all age groups. In a large epidemiologic study from Korea involving 9,243 subjects, Kim and his colleagues reported that the prevalence of COPD was 17.2 % among subjects older than 45

years[10]. There is plenty of information on the prevalence and burden of COPD from the developed countries. Such an assessment is rather scarce from most of the developing world.

The prevalence of COPD reported in different population based studies from India is highly variable[11]. The prevalence rates in male subjects of 2.12% to 9.4% in studies reported from the North are generally higher than 1.4% to 4.08% reported from South India. The respective ranges for female subjects vary from 1.33% to 4.9% in the North and from 2.55% to 2.7% in South India. For epidemiological assessment, the rounded-off median prevalence rates were assessed as 5 percent for male and 2.7 percent for female subjects of over 30 years of age[11]. The disease is distinctly more common in males.

The prevalence was found to increase with increasing age, especially n the males, in those with more than 20 pack–yrs of smoking and in low income subjects. The male to female ratio had varied from 1.32:1 to 2.6:1 in different studies with a median ratio of 1.6:1[11].

RISK FACTORS

A. Genetic risk factor:

a rare recessive severe hereditary deficiency of alpha-1 antitrypsin[14], a major circulating inhibitor of serine proteases, most commonly seen in individuals of Northern European origin[15].

B. Exposure to environmental particles:

- Tobacco smoke:

Cigarette smokers have a greater annual rate of decline in FEV1 and a greater COPD mortality rate than non smokers[16,17]. Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk[18]. Passive exposure to cigarette smoke may also contribute to respiratory symptoms[19] and COPD[20] by increasing the lungs' total burden of inhaled particles and gases[21,22].

- Occupational dusts organic and inorganic Chemicals:

A statement published by the American Thoracic Society concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD[23].

- Indoor and Outdoor Air Pollution:

The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings and high levels of urban pollution is an important risk factor for COPD continues to grow[24-30]. This has been proved by many case-control studies[29.30] and other robustly designed studies .

C. Gender:

Studies from developed countries[31] show that the prevalence of the disease is now almost equal in men and women. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men[32-34].

D. Infection:

A history of severe childhood respiratory infection has been associated with COPD[35-37].

E. Low birth weight:

F. Socioeconomic Status:

The risk of developing COPD is inversely related to socioeconomic status [38-40].

G. Poor nutritional status

H. Co morbidities

SYMPTOMS

Key symptoms include: Patient is usually a Long-time heavy smoker who presents with anyone of the following

- Long-term (chronic) cough.
- Chronic mucus (sputum) production
- Morning "smoker's cough"
- At least one episode of "bronchitis" every winter
- Repeated episodes of acute bronchitis
- Wheezing and Shortness of breath that is persistent and gets worse, occurs during exercise, and gets worse during respiratory infections
- Shallow cough with the feeling that something is stuck inside the chest

Patients may have a rapid, sometimes sudden, and prolonged increase in symptoms (cough, amount of mucus, and/or shortness of breath), especially if the COPD is mainly chronic bronchitis. This is called a COPD exacerbation.

PATHOPHYSIOLOGY OF COPD

Quantitative evidence of increased expiratory flow resistance in emphysema was first obtained in one patient by Neergard and Wirz in 1927[41]. In 1934, Christie described elastic properties or distensibility of the lung in emphysema[42]. The "golden age" of pulmonary macrophysiology, extending from about the 1960s to the 1980s provided new insights regarding the determinants of flow limitation at the levels of the airway and parenchyma. Corbin and coworkers showed that smoking was associated with the loss of lung recoil pressure and with increased static lung volumes (RV, FRC, and TLC), even among individuals who had relatively normal FEV1[43]. Up to a point, these changes appeared reversible with smoking cessation.

COPD, or chronic obstructive pulmonary disease, is a progressive inflammatory disease connecting the airways, lung parenchyma, and vasculature. It causes the damage and remodeling of the airways and lung tissue. The inflammatory process is a driving aspect in the pathophysiology of COPD. Recent verification suggests that the inflammatory response results in a number of effects,

including an arrival of inflammatory cells such as macrophages, neutrophils and lymphocytes. Thickened airways and structural changes such as increased smooth muscle and fibrosis may also be manifested.

Cigarette smoking causes an inflammatory response in the lungs. This response does not cease with the removal of the stimulus, but progresses for an unlimited period of time. These processes result in emphysema, chronic bronchitis, or both. Emphysema begins with a small airway disease and progresses to alveolar destruction, with a predominance of small airway narrowing and mucous gland hyperplasia.

The basic pathophysiologic process in COPD consists of increased resistance to airflow, loss of elastic recoil and decreased expiratory flow rate. The alveolar walls frequently break because of the increased resistance of air flows. The hyper inflated lungs flatten the curvature of the diaphragm and enlarge the rib cage. The altered configuration of the chest cavity places the respiratory muscles, including the diaphragm, at a mechanical disadvantage and impairs their force-generating capacity. Consequently, the metabolic work of breathing increases and the sensation of dyspnea heightens.

Hogg has focused on the importance of *small airway obstruction*, most recently showing that airway remodeling and wall thickening, presence of

inflammatory mucous exudates, and B cell and CD8 T cell inflammation are all associated with severity of COPD and progression of the disease[44]. Christie, Thurlbeck, and others have championed emphysema as the dominant pathology accounting for abnormal physiology, and have shown, for example, that in a subgroup of patients, the relationship between flow and recoil pressure is indeed normal. While many important insights came from this line of investigation, to this day we still do not understand the relative contribution of small airway obstruction versus emphysema in an individual patient, nor the potential relationship between these two lesions. This line of investigation is still fruitful, particularly with the ongoing revolution in imaging.

THE ELASTASE:ANTIELASTASE HYPOTHESIS

Just over 40 years ago, two lines of evidence, one experimental and one clinical, suggested that emphysema is caused by destruction of elastic fibers by elastases. The first was by Laurell and Eriksson who, in 1963, described five patients with deficiency of α-1AT, the primary inhibitor of the neutral serine proteinase neutrophil elastase (NE). Three of these five patients had emphysema[45]. The second came in 1965 when Gross and coworkers instilled papain into the lungs of rodents in an attempt to produce granulomas. Instead they found emphysema[46].

Subsequently, investigators have instilled a variety of proteinases into animal lungs. Kuhn and colleagues[47], Senior and coworkers[48], Janoff and associates[49], and Snider and colleagues[50] were among the group of investigators who subsequently demonstrated that only elastolytic proteinases—including pancreatic elastase and the more relevant human neutrophil elastase (HNE)—caused emphysema. Hoidal's group showed that proteinase 3[51] also caused destructive lung disease. These seminal experiments formed the basis for the elastase : antielastase hypothesis, which states that the relative balance between elastases and their inhibitors determines the susceptibility of the lung to the destruction characteristic of emphysema.

INFLAMMATION–EXTRACELLULAR MATRIX TURNOVER

A classic study by Damiano and coworkers correlated the presence of HNE with COPD using immunogold staining[52]. However, other studies actually showed a negative correlation between emphysema and HNE or neutrophil number[53, 54]. As discussed above, macrophages are abundant in COPD, yet the capacity of the macrophage to degrade elastin and hence contribute to disease pathogenesis was unproven until Senior and colleagues demonstrated that macrophages produce elastolytic matrix metalloproteinases[55,56], and Chapman and coworkers found elastolytic cysteine proteinases[57].

Retamales and colleagues[58] found that even in end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response. This suggests that the mechanisms of cigarette smoke–induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation. Moreover, this study suggests that multiple inflammatory (and likely structural) cells interact to cause COPD, and that focusing on single cells and proteinases in isolation will not provide a comprehensive understanding of the disease process.

Cigarette smoke causes constitutive macrophages to produce MMP-12, which, in turn, cleaves elastin into fragments chemotactic for monocytes. This positive feedback loop perpetuates macrophage accumulation and lung destruction. The concept that proteolytically generated elastin fragments mediate monocyte chemotaxis was proven by Senior and coworkers[59] and Hunninghake and colleagues[60].At the very least, this study demonstrates a critical role for macrophages in the development of emphysema and unmasks a proteinase-dependent mechanism of inflammatory cell recruitment. Of note, last year Grumelli and coworkers found that human CD8+ T cells derived from patients with COPD generate interferon (IFN)-γ–inducible chemokines that also function to upregulate expression of human macrophage MMP-12[61]. Studies by Churg and

coworkers demonstrate that acute neutrophil inflammation secondary to smoking is related to MMP-12–dependent tumor necrosis factor (TNF) shedding [62].

OXIDANT–ANTIOXIDANT BALANCE

Cigarette smoke and inflammatory cells have the capacity to produce reactive oxygen species, and they have been postulated to play a variety of roles in the pathogenesis of emphysema. One intriguing finding was that cigarette smoke can oxidize a methionine residue in the reactive center of A1PI, inactivating A1PI and thus altering the elastase:antielastase balance. Oxidants cannot degrade extracellular matrix but might modify elastin, making it more susceptible to proteolytic cleavage.

Recently, Barnes and colleagues have found that cigarette smoke oxidizes and inactivates histone deacetylase 2 (HDAC2), which acts to counter histone acetylase (HAT)[63]. Acetylation of histone unwinds chromatin, allowing transcriptional complexes to bind to DNA. Thus, in the absence of HDAC2, RNA polymerase II and NF-kβ form a proinflammatory transcription complex. Finally, reactive oxygen species may also promote apoptosis of structural cells, a recent concept for initiation of emphysema.

APOPTOSIS

Kasahara and colleagues found that exposure to agents that initiate endothelial cell death (via VEGFRII inhibition) leads to non inflammatory airspace enlargement[64]. Nagai and coworkers then found that epithelial cell death (via caspase 3 delivery) also causes emphysema[65]. As mentioned above, the loss of an acinar unit results from the destruction of both the extracellular matrix (ECM) and the structural cells. These models suggest that death of structural cells may be an initiating event, with subsequent release of matrix-degrading proteinases. Whether this occurs in human COPD as a primary event is uncertain,

INEFFECTIVE REPAIR

The ability of the adult lung to repair damaged alveoli appears limited. In fact, as we define genetic predisposition to COPD, we speculate that smoking routinely leads to inflammation and lung damage, and those at risk lack the capacity to repair this damage. In emphysema, aberrant alveolar and extracellular matrix repair results in coalesced and enlarged airspaces with depleted and disordered parenchymal elastic fibers, and excess and abnormally arranged collagen.

SYSTEMIC INVOLVEMENT IN COPD

The pathogenesis and clinical manifestations of COPD are not restricted to pulmonary inflammation and structural remodeling. Rather, this disorder is associated with clinically significant systemic alterations in biochemistry and organ function. The systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute-phase proteins. Indeed, an impaired endogenous oxidant-antioxidant balance[66-68] has been reported in patients experiencing exacerbations of COPD, and others have observed altered circulating levels of several cytokines and adhesion molecules in patients with stable disease. As in other chronic inflammatory conditions, weight loss, muscle wasting, and tissue depletion are commonly seen in COPD patients.

Wasting is a generally occurring manifestation in a wide variety of different chronic conditions and can be considered to be an important systemic manifestation as a loss of > 40% of actively metabolizing tissue is incompatible with life[69-70]. The body cell mass (BCM) represents the actively metabolizing (organs) and contracting (muscles) tissue. This BCM cannot be measured directly. Changes in BCM can be clinically recognized by decrease in body mass index (BMI) in general and by loss in fat-free mass (FFM) in particular. In a retrospective study of 400 patients with COPD, Schols et al[71] demonstrated that

low body mass index (BMI), age, and low PaO_2 were significant independent predictors of increased mortality rates. After stratification of the group into BMI quintiles, a threshold value of 21 kg/m^2 was identified below which the mortality risk was clearly increased.

SPIROMETRIC CLASSIFICATION OF COPD SEVERITY

The present widely accepted classification of COPD is mainly based on the FEV1 values[1]. It is as follows

Stage I: Mild COPD –

Characterized by mild airflow limitation (FEV1/FVC < 0.70; FEV1 >/= 80% predicted). Symptoms of chronic cough and sputum production may be present. Patients are usually unaware of the illness.

Stage II: Moderate COPD –

Characterized by worsening airflow limitation (FEV1/FVC < 0.70; 50% </= FEV1 < 80% predicted), with shortness of breath typically developing on exertion with or without cough and sputum production. This is the stage at which patients typically seek medical attention.

Stage III: Severe COPD –

Characterized by further worsening of airflow limitation (FEV1/FVC < 0.70; 30% </= FEV1 < 50% predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patients' quality of life.

Stage IV: Very Severe COPD –

Characterized by severe airflow limitation (FEV1/FVC < 0.70; FEV1 < 30% predicted or FEV1 < 50% predicted plus the presence of chronic respiratory failure). Respiratory failure is defined as arterial partial pressure of oxygen (PaO2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

LIMITATIONS OF SPIROMETRIC CLASSIFICATION

The spirometric classification, though good in many ways is not full proof for the assessment of severity of COPD. The FEV_1 is essential for the diagnosis and quantification of the respiratory impairment resulting from COPD[72-74]. In addition, the rate of decline in FEV_1 is a good marker of disease progression and mortality[75,76]. However, the FEV_1 does not adequately reflect all the systemic manifestations of the disease. For example, the FEV_1 correlates weakly with the

degree of dyspnea[77], and the change in FEV_1 does not reflect the rate of decline in patients' health[78]. More important, prospective observational studies of patients with COPD have found that the degree of dyspnea[79] and health-status scores[80] are more accurate predictors of the risk of death than is the FEV_1. Thus, although the FEV_1 is important to obtain and essential in the staging of disease in any patient with COPD, it alone as the sole parameter of severity does not throw light on the systemic involvement and progession of the disease.

BODE INDEX

Due to reasons above stated, researchers described a new index – BODE index, for the comprehensive evaluation of patients with COPD. This multisystem grading index has four variables.

- Body mass index
- Obstruction to airflow (FEV1)
- Dyspnea (MMRC dyspnea scale)
- Effort tolerance (6 minute walk test)

Each variable in the index correlates independently with the prognosis of COPD, is easily measurable, and serves as a surrogate for other potentially important variables. In the BODE index, two descriptors of systemic involvement were included: the body-mass index and the distance walked in six minutes. Both are simply obtained and independently predict the risk of death[81-83]. It is likely that they share some common underlying physiological determinants, but the distance walked in six minutes contains a degree of sensitivity not provided by the body-mass index. The six-minute walk test is simple to perform and has been standardized[84]. Its use as a clinical tool has gained acceptance, since it is a good predictor of the risk of death among patients with other chronic diseases, including congestive heart failure[84] and pulmonary hypertension. Indeed, the distance walked in six minutes has been accepted as a good outcome measure after interventions such as pulmonary rehabilitation.

The body-mass index was also an independent predictor of the risk of death and was therefore included in the BODE index. We evaluated the independent prognostic power of body-mass index in our cohort using different thresholds and found that values below 21 were associated with an increased risk of death, an observation similar to that reported by Landbo and coworkers in a large population study[79].

The Global Initiative for Chronic Obstructive Lung Disease and the American Thoracic Society recommend that a patient's perception of dyspnea be included in any new staging system for COPD. Dyspnea represents the most disabling symptom of COPD; the degree of dyspnea provides information regarding the patient's perception of illness and can be measured. The MMRC dyspnea scale is simple to administer and correlates with other dyspnea scales and with scores of health status[80]. Furthermore, in a large cohort of prospectively followed patients with COPD, which used the threshold values included in the BODE index, the score on the MMRC dyspnea scale was a better predictor of the risk of death than was the FEV_1.

The BODE index combines the four variables by means of a simple scale. Weighting the variables included in the index did not improve the predictive power of the BODE index. Most likely, it failed to do so, because each variable included has already proved to be a good predictor of the outcome of COPD.

MATERIALS AND METHODS

SETTING

Institute of internal medicine

Madras Medical college and Government General hospital

Chennai – 600 003

INSTITUTIONAL ETHICS COMMITTEE APPROVAL

Obtained

STUDY DESIGN

To evaluate the BODE index as a predictor of hospitalization and severity of systemic involvement in patients with Chronic Obstructive Pulmonary Disease, a cross sectional study design was chosen.

PERIOD OF STUDY

May 2007 to July 2008

SAMPLE SIZE

Cases : 90 ; controls : 30

INCLUSION CRITERIA

- Male patients with symptoms suggestive of COPD as cases
- Male patients who came for master health check up as controls

EXCLUSION CRITERIA

- Spirometry proved bronchial asthma defined as an increase in the FEV_1 of more than 15 percent above the base-line value or of 200 ml after the administration of a bronchodilator
- recent myocardial infarction < 4months
- unstable angina
- congestive heart failure (NYHA class III or IV)
- inability to perform spirometry or 6 minute walk test
- Unrelated life threatening major illness
- liver disease
- patients with acute exacerbation

STUDY PROTOCOL

A total of 120 patients who attended our outpatient clinic at the Madras Medical College and Government General Hospital, Chennai were enrolled into the study. Of these, 90 patients with symptoms suggestive of COPD were selected as cases and 30 patients who came for Master health checkup were selected as controls.

The patients with the following diagnostic criteria (according to the GOLD guidelines) were defined as having COPD

1. the presence of cough and sputum production for at least 3 months in each of the two consecutive years
2. exertional dyspnoea
3. physical examination showing
   (a) Signs of airflow limitation like prolonged expiration and expiratory wheeze which is not fully reversible;
   (b) Signs of hyperinflation
4. Spirometry showing post bronchodilator FEV1/FVC ratio < 0.70

The present analysis was restricted to male patients only, who met the acceptability and reliability criteria of the American Thoracic Society to improve the diagnostic accuracy as sex may be a confounding factor in many of the parameters assessed.

For each enrolled subject, detailed history of smoking, personal and family medical histories were obtained. On the day of enrollment, height and weight were measured twice during the examination. Weight was measured to the nearest 100 grams with bare foot. Height was measured to the nearest mm with the stadometer. Body mass index (BMI) was calculated by the formula.

$$BMI = \text{Weight in Kgs} / (\text{Height in Ms})^2$$

Spirometry was performed with an equipment that met the American thoracic society performance criteria, in each of the cases on enrollment into the study and 20 minutes following the administration of salbutamol nebulisation. To adjust for the height, sex, age and sex published prediction equations for forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were used. FEV1 and FVC were calculated. The procedure was repeated on 2 occasions and the average value was taken.

A detailed history of the dyspnea experienced by the patient was taken. MMRC dyspnea scale was used to score the patients dyspnea. Six minute walk test was performed twice with a gap of 30 minutes rest in between and the average was taken. Patients were asked to walk on a level ground for maximum possible distance within a duration of 6 minutes. Periods of rest taken, was also included in the 6 minutes test period.

The BODE index was calculated for each patient using the body mass index, the threshold value of FEV1, the distance walked in 6 min, and the score on the modified Medical Research Council (MMRC) dyspnea scale. The patients received points ranging from 0 (lowest value) to 3 (maximal value). For body mass index the values were 0 (>21) or 1 (<21). The scores for FEV1 were 0 (more than or equal to 65%), 1 (50 – 64%), 2 (36 – 49%) and 3 (less than or equal to 35%). The 6 minute walk test scores were 0 (> 350 ms), 1 (250 – 350 ms), 2 (150 – 249 ms) and 3 (< 150 ms). The MMRC dyspnea class 0 and I were given 0 points, class II – 1 point, class III – 2 points and class IV – 3 points. The points for each variable were added, so that the BODE index ranged from 0 to 10 points in each patient. The BODE score of 0 – 2 was taken as mild COPD. Scores between 3 – 5 was considered as moderate disease and those more than or equal to 6 was considered as severe COPD.

MMRC dyspnea scale

Grade 0 – no dyspnea / only on severe exertion

Grade 1 – dyspnea on hurrying / walking up a hill

Grade 2 – walks slower than normal at level/ pause while walking on level ground

Grade 3 – stops for breath after walking 100 yards/few mins on level ground

Grade 4 – too breathless to leave the house/ dyspnea on dressing

BODE INDEX:

BODE score	0	1	2	3
FEV1	>/= 65 %	50 – 64%	36 – 49%	< /= 35%
6 min walk test	>350 ms	250 – 349ms	150 – 249 ms	<149 ms
Dyspnea scale	0 – 1	2	3	4
BMI	> 21 kg/m^2	<21 kg/m^2		

Mild COPD → 0 – 2

Moderate COPD → 3 – 5

Severe COPD → >/= 6

A detailed history regarding number of days of hospital admission in the last two years was obtained from the patients response to the question "how many days have you been admitted in hospital in the past 2 years due to reasons related to COPD ?" Patient's discharge cards were also reviewed.

A standard 12 lead ECG was taken for each of the individual patients. QRS axis was determined by plotting the QRS potentials on a graph with lead I as X axis and aVF as Y axis. – 30 to + 90 was considered as normal axis, – 30º to – 90º as left axis , +90º to +180º as right axis and – 90º to + 180º was considered as north west axis. Echo cardiography was performed using 2D echo in the institute of cardiology, Madras Medical College. Ejection fraction and pulmonary pressure gradient was assessed. Pulmonary artery hypertension was graded as mild, moderate and severe.

Hemoglobin estimation was performed according to the routine standards using an automated analyzer at the biochemistry lab attached to the institute of biochemistry, Madras Medical College and Government General Hospital. CRP was estimated in the lab using the latex agglutination method. Agglutination at a dilution of 6 or less was considered as negative result. Positive result was expressed as the dilution at which agglutination occurred.

FINANCIAL SUPPORT: nil

CONFLICT OF INTEREST: nil

STATISTICAL ANALYSIS

Statistical analysis was carried out in all the 120 subjects (including 90 COPD patients and 30 controls) after categorizing the variable. Baseline data was collected from patients without and with mild, moderate and severe COPD. Ages, body mass index, days of hospitalization, mean hemoglobin concentration, QRS axis, ejection fraction, pulmonary hypertension, serum albumin concentration, and CRP of all subjects were the parameters analyzed.

The significance of difference in means between two groups was analyzed using the one way ANOVA F-test and the significance of difference in proportions by the Chi square test. Multiple comparisons were done by fishers least significant difference (LSD) t-test. Statistical significance was taken when the p value was less than 0.05.

Statistical analysis was carried out using the standard formula. Microsoft excel 2007 and SPSS (statistical package for social sciences)version 13 software was used for data entry and analysis.

RESULTS AND OBSERVATIONS

A total of 120 patients including 90 patients with COPD as cases and 30 healthy individuals as controls were enrolled in the study. All the cases and controls were males. Among patients with COPD, there were 32 (35.56%) patients who had mild COPD with a BODE score between 0 – 2. Moderate (BODE score of 3 – 5) and severe COPD (BODE score more than or equal to 6) groups had 29 patients (32.22%) each.

Table 1: Age wise distribution in years

Group	N	Mean (yrs)	Std. deviation	One way ANOVA F-test
Control	30	54.70	5.603	F=4.440 P=0.005 significant
Mild (0-2)	32	53.47	7.362	
Moderate (3-5)	29	55.00	8.627	
Severe (>/=6)	29	59.93	7.606	
Total	120	55.71	7.679	

The average age of participants in the study was 55.71 years. Among the COPD patients, BODE index was found to increase with age with the mild group having a mean age of 53.47 years, moderate group 55.00 years and the severe group with 59.93 years as the mean age. The difference was statistically significant with a P value of 0.005.

Table 2: Smoking status

Groups	Smoker				Total N	Pearson chi square test
	Yes		No			
	N	%	N	%		
Control	12	40.0	18	60	30	X^2 -19.352 P =0.000 significant
Mild	14	43.7	18	56.3	32	
Moderate	19	65.5	10	34.5	29	
Severe	26	89.7	3	10.3	29	
Total	71	59.2	49	40.8	120	

The proportion of smokers was higher in the higher BODE index group compared to the lower index group. There was no significant difference between the control group and the lower score group. Thus smoking status had a positive risk correlation with higher BODE index (P = 0.000).

Table 3: Smoking in pack years

Group	N	Mean (pack yrs)	Std. deviation	Oneway ANOVA F test
Control	30	4.55	5.603	F = 26.936 P = 0.000 Significant
Mild	32	7.42	7.362	
Moderate	29	15.07	8.627	
Severe	29	26.90	7.606	
Total	120	13.26	7.679	

The study revealed that the BODE score was significantly associated with the number of pack years of smoking. It was 4.55 pack yrs in controls, 7.42 pack yrs in mild cases, 15.07 in moderate and 26.90 in severe cases. On multiple comparison by LSD the difference between control group and mild group was not statistically significant but that of the other 2 groups were highly significant (P = 0.000).

Table 4: Body Mass index

Group	N	Mean (kg/m^2)	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	24.294	2.544	F = 11.431 P = 0.000 Significant	1Vs2,3,4 2Vs1,4 3Vs1,4 4Vs1,2,3 P = 0.05
Mild	32	22.476	2.455		
Moderate	29	21.711	2.552		
Severe	29	20.260	3.212		
Total	120	22.210	3.035		

The average BMI of the patients in our study was 22.21 kg/m^2. The control group had a BMI of 24.294 kg/m^2 with a standard deviation of 2.544. The BMI was found to be significantly lower in patients with COPD. It was 22.476 kg/m2 (standard deviation –2.455) in the mild group, 21.711 (std. deviation – 2.552) in the moderate group and 20.260 (std. deviation – 3.212) in the severe group. On multiple comparisons the significance between mild and moderate groups was not found to be significant. All other comparisons showed significant difference.

Table 5: Duration of hospital stay over last 2 years (days)

Group	N	Mean (days)	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	0.07	0.365	F = 75.340 P = 0.000 Significant	1Vs3,4 2Vs3,4 3Vs1,2,4 4Vs1,2,3 P = 0.05
Mild	32	0.13	0.492		
Moderate	29	3.17	2.929		
Severe	29	16.00	9.177		
Total	120	4.68	8.041		

The study results showed that a higher BODE score was associated with a higher incidence of hospital stay due to reasons related to COPD, over the past 2 years. The control group and the mild COPD group did not have any significant hospital admission during the past 2 years. The average duration of stay in the moderate study group was 3.17 days while it was 16 days in the group with severe COPD according to the BODE score. Both these values were found to be significant on multiple comparisons to other groups.

Table 6: Hemoglobin concentration in gm/ dL

Group	N	Mean (gm/dL)	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	11.040	1.305	F = 50.733 P = 0.000 Significant	1Vs3,4 2Vs3,4 3Vs1,2,4 4Vs1,2,3 P = 0.05
Mild	32	10.713	1.439		
Moderate	29	12.176	1.566		
Severe	29	14.869	1.460		
Total	120	12.153	2.168		

Comparing the hemoglobin values in various groups of the study it was found that the mean hemoglobin concentration was lower (10.713 gm/dL) in those patients with COPD compared to controls (11.04 gm/dL). However this correlation was not found to be significant on multiple comparisons trial. The values in the other 2 groups were significantly higher (moderate – 12.176 gm/dL and severe 14.869 gm/dL). This was found to be statistically significant at a P value of 0.05.

Table 7: QRS axis in ECG and BODE score

Group	ECG axis								Pearson chi square test
	Normal		RAD		LAD		North West axis		
	N	%	N	%	N	%	N	%	
Control	26	86.7%	0	0 %	4	13.3%	0	0 %	df= 9.0 P = 0.000 significant
Mild	27	84.4%	0	0 %	5	15.6%	0	0 %	
Moderate	20	69.0%	9	31.0%	0	0 %	0	0 %	
Severe	1	3.4 %	25	86.2%	0	0 %	3	10.3%	
Total	74	61.7%	34	28.3%	9	7.5 %	3	2.5 %	

The QRS axis was found to vary among the different groups studied. The control group had 26 patients with normal axis and 4 with left axis. Mild COPD group had 27 patients with normal axis and 5 patients with right axis deviation. Out of 29 patients in moderately severe COPD group 20 had normal axis and 9 had right axis deviation. In patients with the highest BODE score 1 patient had normal axis, 34 had right axis deviation, 9 with left axis deviation and 3 had North West axis.

Table 8: Ejection fraction Vs BODE score

Group	N	Mean (%)	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	73.43	8.597	F = 85.476 P = 0.000 Significant	1Vs2,3,4 2Vs1,3,4 3Vs1,2,4 4Vs1,2,3 P = 0.000
Mild	32	65.06	3.089		
Moderate	29	56.45	6.500		
Severe	29	47.31	7.177		
Total	120	60.78	11.689		

The Ejection fraction varied considerably among various groups in the study. For the control group, mean EF was 73.43% (std. deviation 8.597). The mean ejection fraction for the other groups were mild COPD group 65.06% (std. deviation 3.089), the moderate COPD group 56.45% (std. deviation 6.500) and the severe group 47.31% (std. deviation 7.177). The difference of mean ejection fractions was significant between the various groups was statistically significant with a P value of 0.000.

Table 9: Pulmonary hypertension and BODE score

Group	pulmonary hypertension								Pearson chi square test
	Normal		mild		moderate		severe		
	N	%	N	%	N	%	N	%	
Control	30	100%	0	0 %	0	0 %	0	0 %	
Mild	32	100%	0	0 %	0	0 %	0	0 %	df= 9.0
Moderate	19	65.5%	8	27.6%	2	6.9 %	0	0 %	P = 0.000 significant
Severe	0	0 %	5	17.3%	17	58.6%	7	24.1%	
Total	81	67.5%	13	10.8%	19	15.8%	7	5.8 %	

This study showed that there was no incidence of pulmonary hypertension in the controls and the group with mild COPD according to BODE scores. In the moderate COPD group 19 patients did not have pulmonary hypertension while 8 showed mild and 2 patients had severe PHT. However in the severe COPD group all patients had PHT with 13 patients having mild PHT, 19 having moderate and 7 patients having severe PHT.

Table 10: Albumin concentration Vs BODE score

Group	N	Mean (gm/dL)	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	3.900	.2901	F = 40.010 P = 0.000 Significant	1Vs3,4 2Vs3,4 3Vs1,2,4 4Vs1,2,3 P = 0.05
Mild	32	3.850	.2664		
Moderate	29	3.462	.4057		
Severe	29	2.997	.4579		
Total	120	3.563	.5084		

Albumin concentration was found to progressively decrease with increase in BODE score. The mean albumin concentrations were 3.900 gm/dL (std. deviation .2901), in the control group, 3.850 gm/dL (std. deviation .4507) in the mild group, 3.462 gm/dL (std. deviation 0.4057) in the moderate group and 3.563 gm/dL (std. deviation 0.5084) in the severe COPD group. The difference was not significant between the controls and patients with mild COPD. However the difference of the moderate and severe COPD groups with the other groups were highly significant (P = 0.000).

Table 11: C reactive protein Vs BODE score

Group	N	Mean	Std. deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control	30	2.60	3.410	F = 85.476 P = 0.000 Significant	1Vs3,4 2Vs3,4 3Vs1,2,4 4Vs1,2,3 P = 0.05
Mild	32	7.31	4.993		
Moderate	29	33.72	18.452		
Severe	29	105.93	53.480		
Total	120	36.35	49.577		

The marker of systemic inflammation the C reactive protein was found to be highest in the group with the highest BODE scores 105.93 (std. deviation 53.48). it was not significantly different between the control(2.60) and the mild COPD (7.13) groups and in the moderate group the titer was 33.72. The difference was statistically significant with a P value of 0.05.

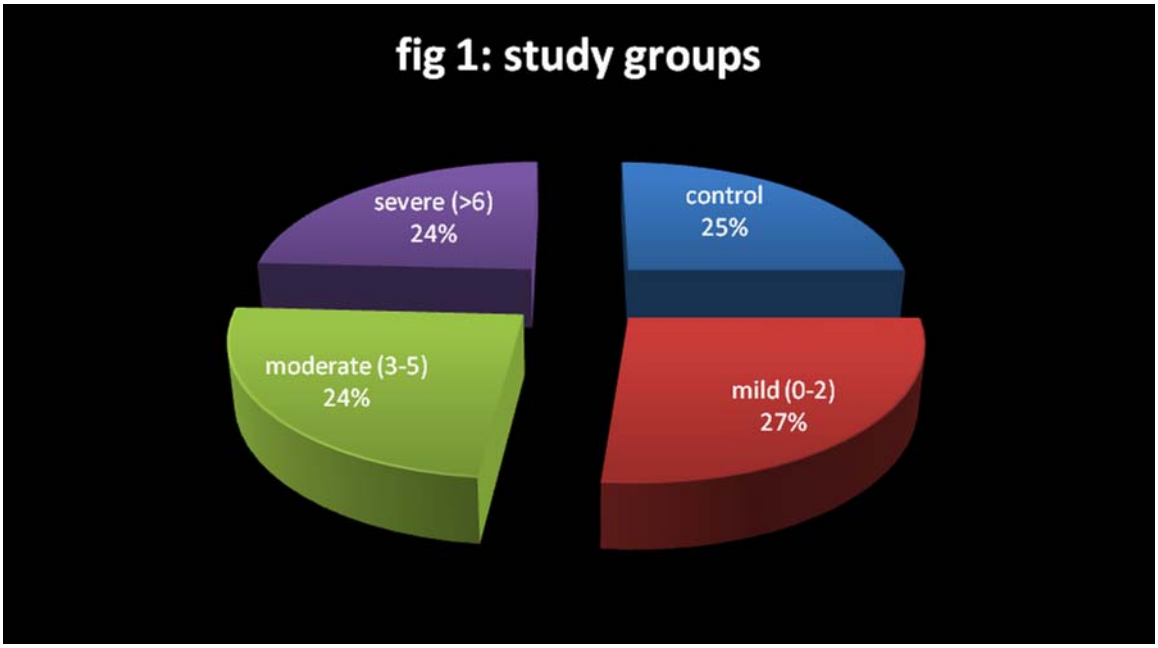


fig 1: study groups
severe (>6)
24%
control
25%
moderate (3-5)
24%
mild (0-2)
27%

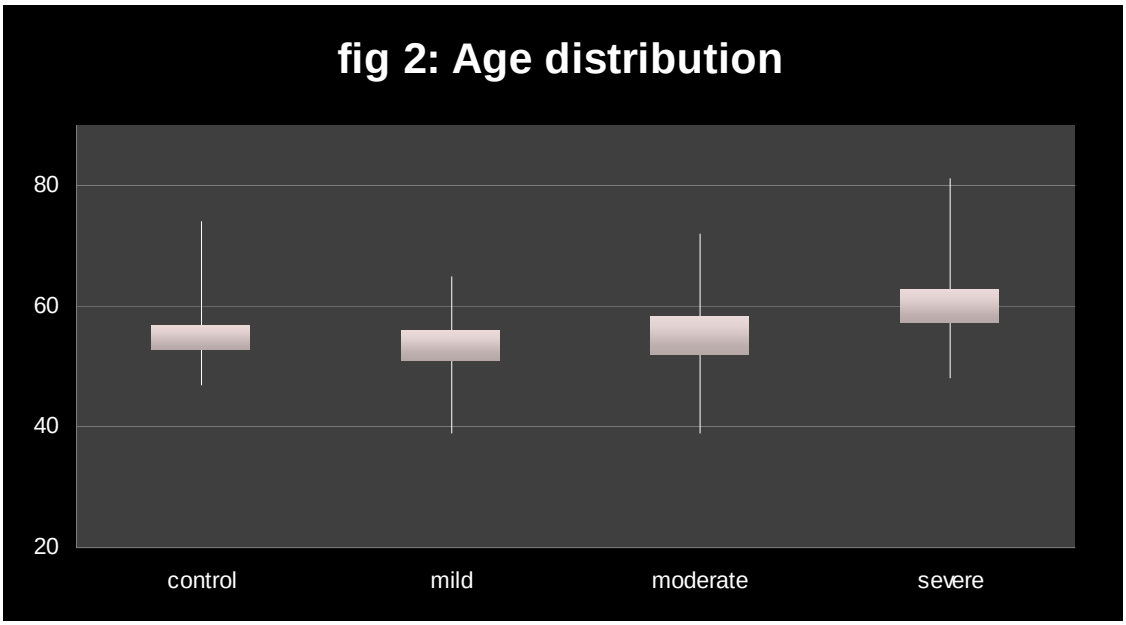


fig 2: Age distribution
80
60
40
20
control
mild
moderate
severe

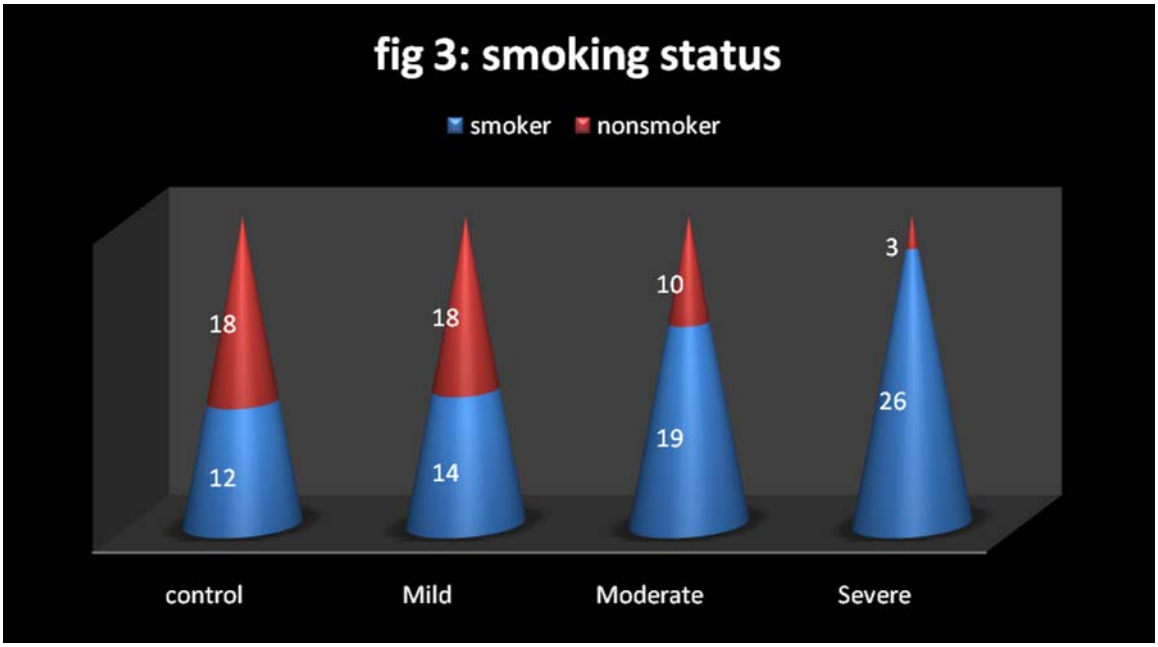


fig 3: smoking status
smoker
nonsmoker
18
12
18
14
10
19
3
26
control
Mild
Moderate
Severe

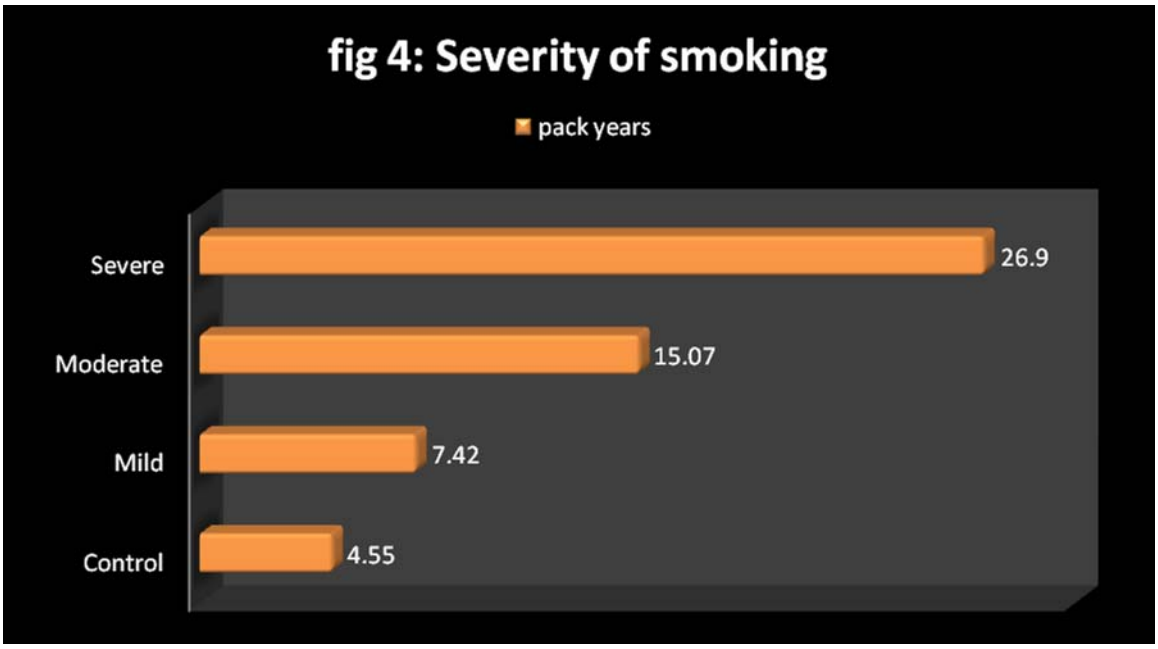


fig 4: Severity of smoking
pack years
Severe
Moderate
Mild
Control
26.9
15.07
7.42
4.55

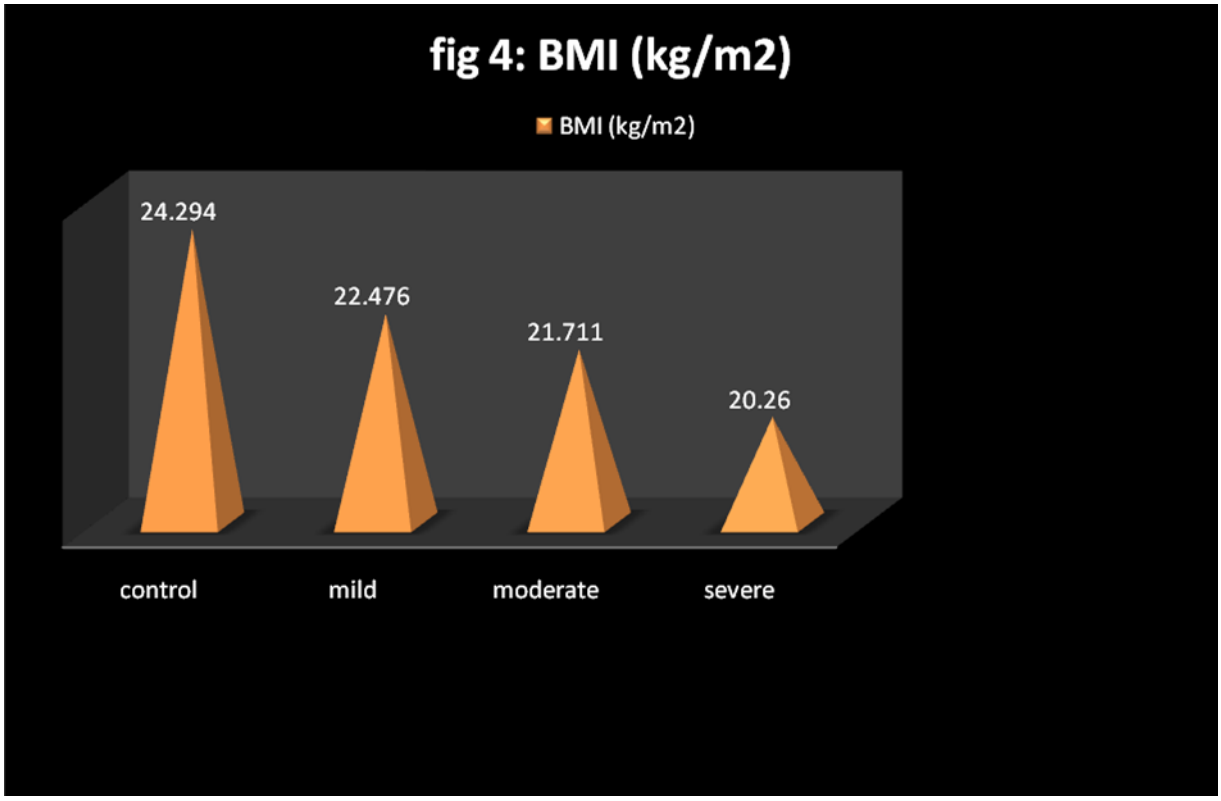


fig 4: BMI (kg/m2)
BMI (kg/m2)
24.294
22.476
21.711
20.26
control
mild
moderate
severe

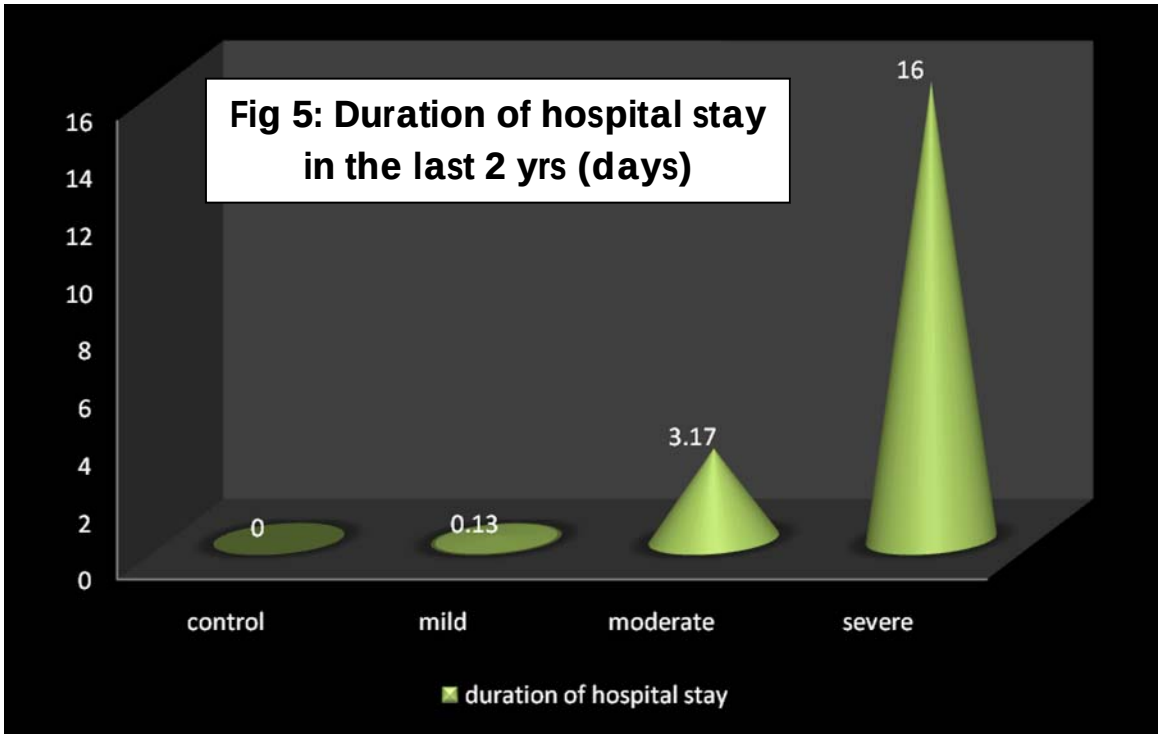


Fig 5: Duration of hospital stay in the last 2 yrs (days)
16
14
12
10
8
6
4
2
0
0
0.13
3.17
16
control
mild
moderate
severe
duration of hospital stay

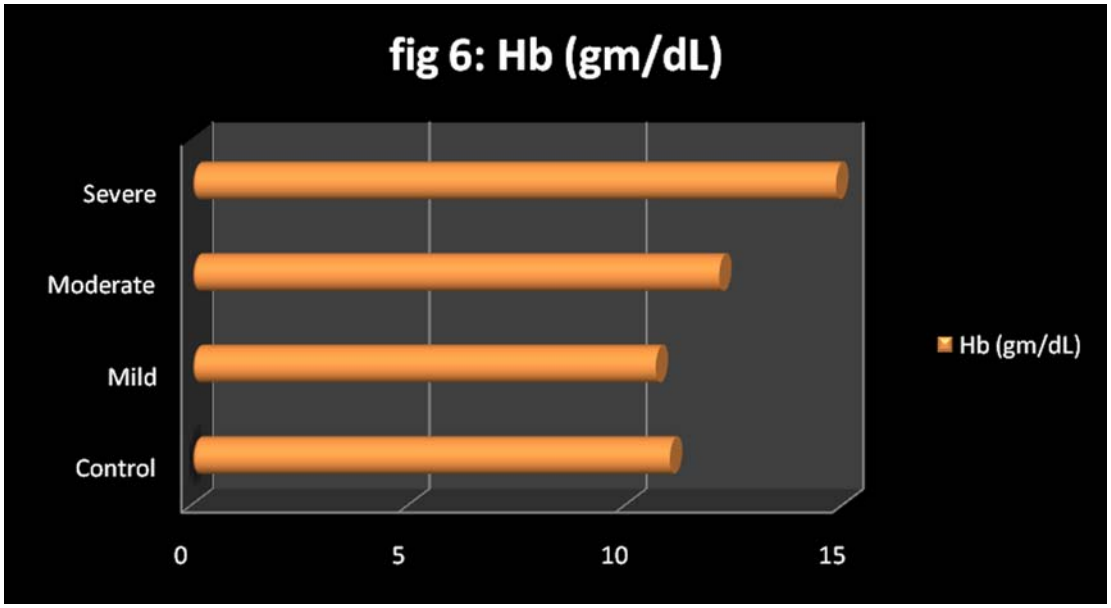
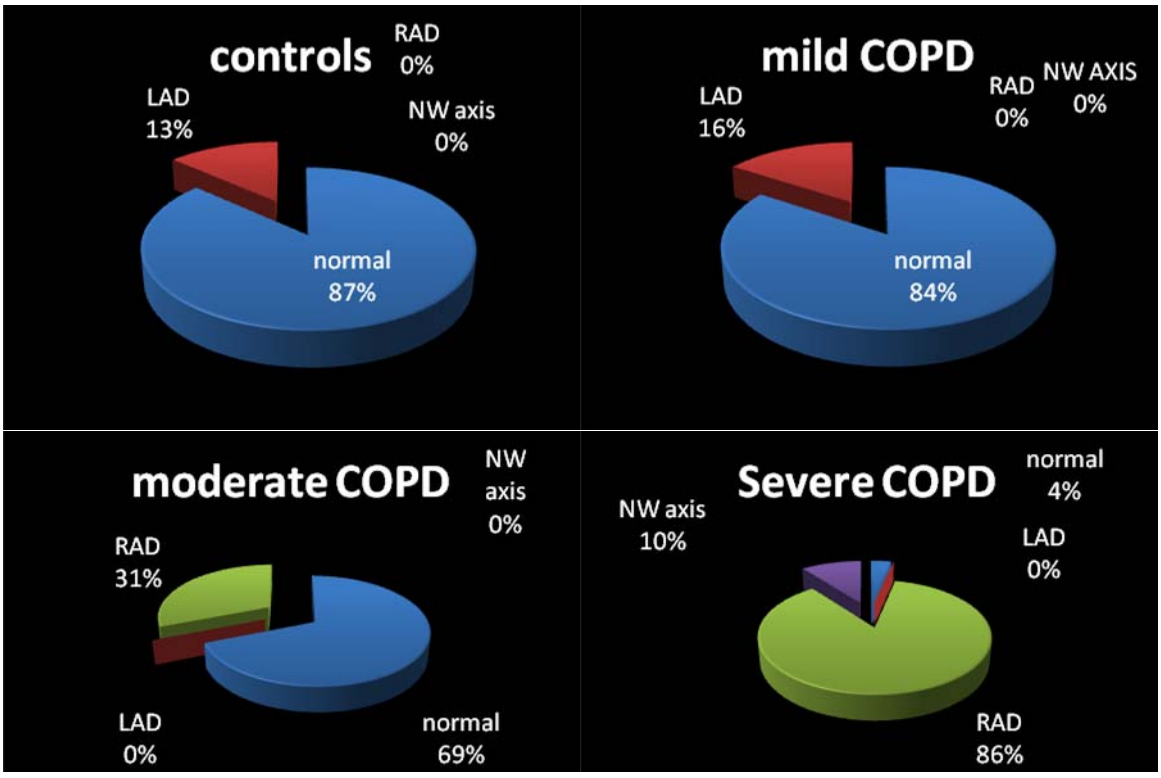


Fig 7: QRS AXIS IN ECG



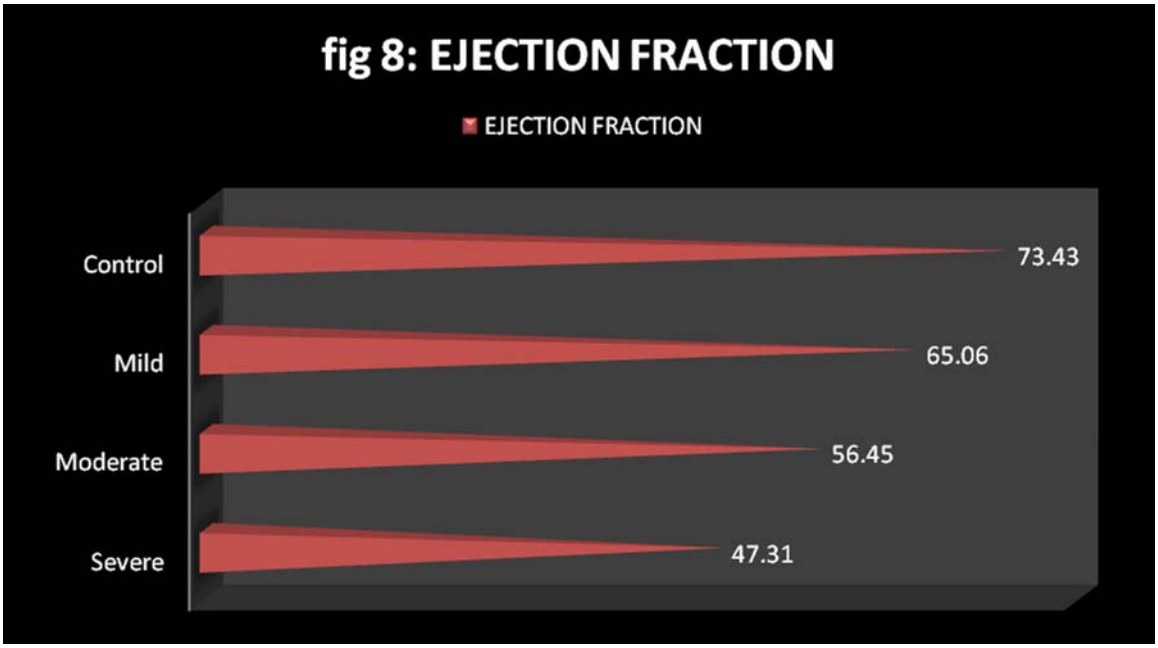


fig 8: EJECTION FRACTION
EJECTION FRACTION
Control
Mild
Moderate
Severe
73.43
65.06
56.45
47.31

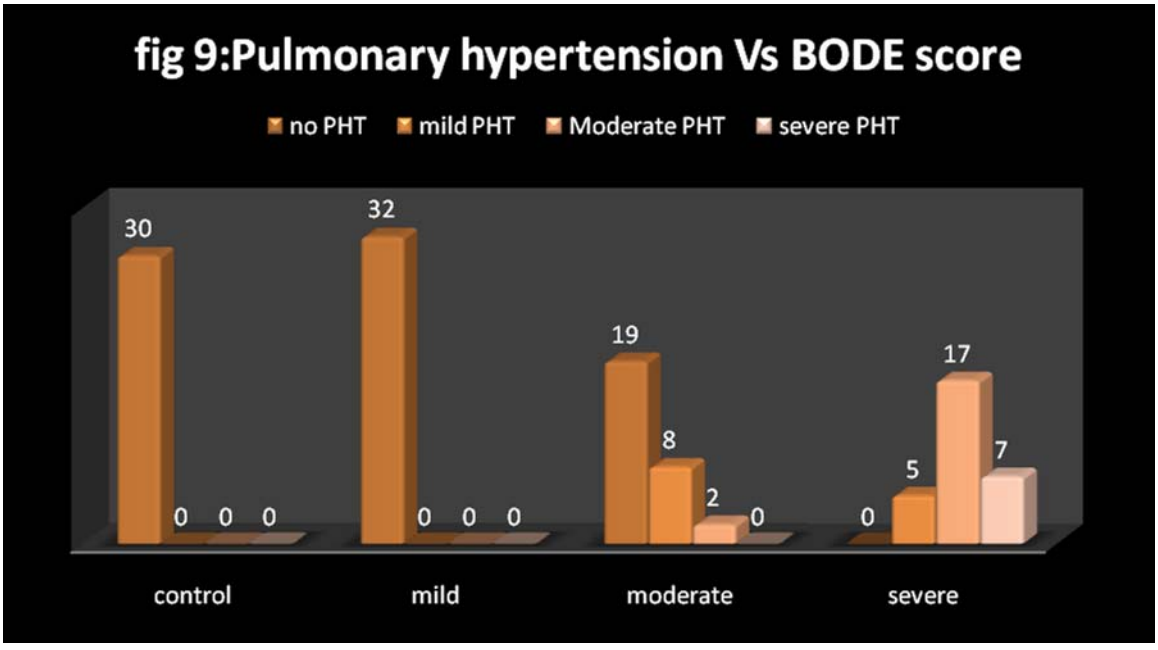


fig 9:Pulmonary hypertension Vs BODE score
no PHT
mild PHT
Moderate PHT
severe PHT
30
0
0
0
32
0
0
0
19
8
2
0
0
5
17
7
control
mild
moderate
severe

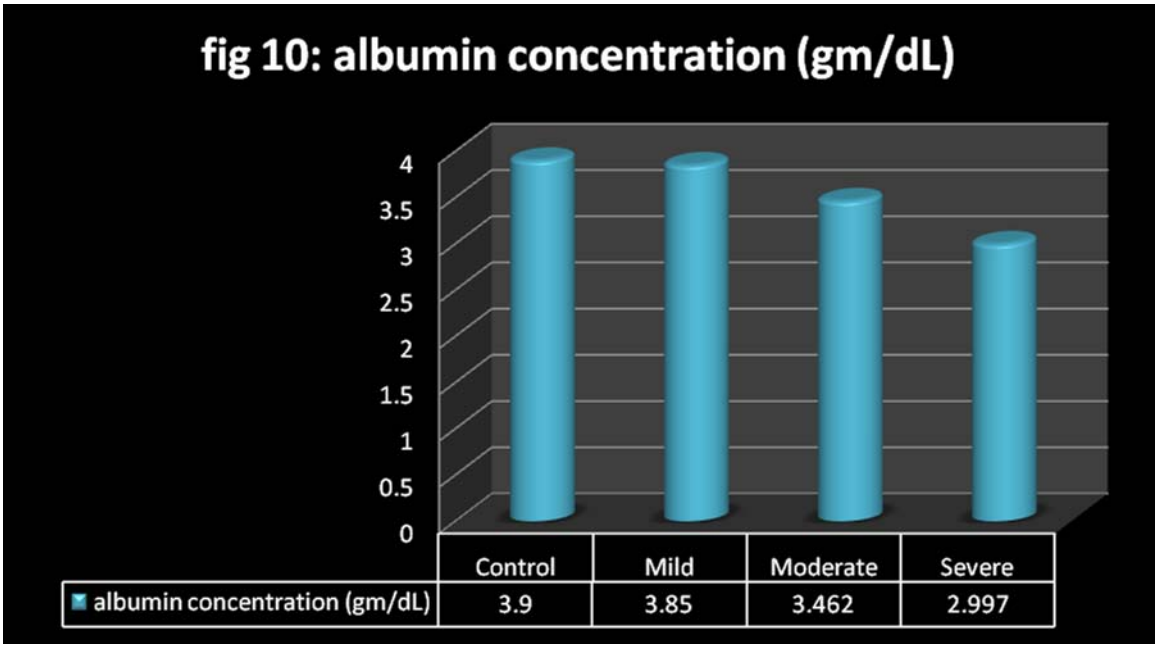


fig 10: albumin concentration (gm/dL)
4
3.5
3
2.5
2
1.5
1
0.5
0
Control
Mild
Moderate
Severe
albumin concentration (gm/dL)
3.9
3.85
3.462
2.997

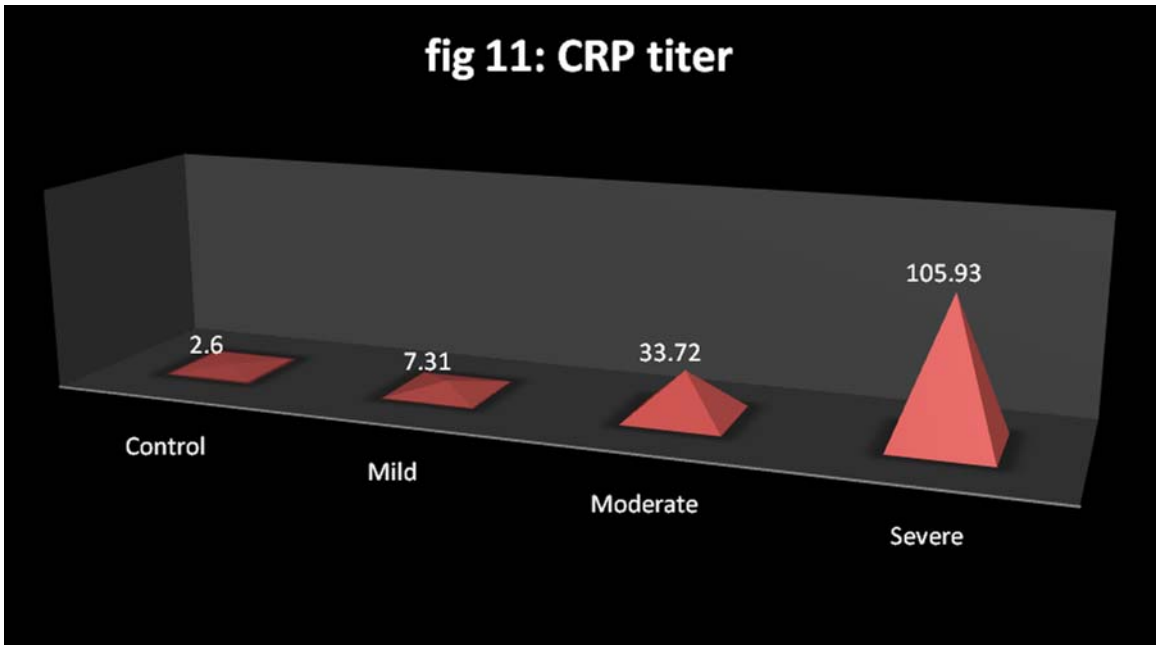


fig 11: CRP titer
2.6
7.31
33.72
105.93
Control
Mild
Moderate
Severe

DISCUSSION

COPD is predicted to be one among the most common killer diseases affecting a large number of individuals by the year 2020. In the recent past, more stress has been given to formulate a simple but effective index for assessing the severity of COPD. Researchers have found that BODE index would fulfill this necessity. But most of the research has been limited to finding the usefulness of the index in predicting the mortality and hospitalization in patients with COPD. In our study we tried to evaluate its usefulness in predicating the severity of COPD in terms of hospitalization, systemic involvement and the level of systemic inflammation. Our research has brought out many results which would have a significant impact in the management of COPD in the future.

We included only male patients in our research, since COPD is more common among male patients. This was aimed at making the study group as uniform as possible. Such a selection would negate the differences in the BODE index among various patients studied, by removing the gender related differences in FEV1, BMI and patient perception of dyspnea.

Studies by Celli etal[5] and Kian-Chung etal[2] has proven that grouping COPD patients into three groups with BODE scores 0 – 2 as first group, 3 – 5 as second and 6 or more as the third group correlates well with severity in terms of

hospitalization and mortality. Hence we have accepted the same classification and grouped the above groups as mild, moderate and severe COPD. Our study individuals were almost equally distributed in the various groups. 30 controls were also selected.

Kian-chung etal[2] and Celli etal[5] has shown in their respective studies that BODE score increases with age. This study also shows a significant increase in the severe and moderately severe group compared to controls. This could be due to the progression of COPD with age. However results from a few other studies [76, 77] do not significant progression with age. This difference is mainly due to the fact that duration of smoking was not proportional to age in those groups unlike in our study.

Results from this study go along with most other studies, in the relationship of smoking to BODE index. Studies by Kian-chung etal[2], Celli etal[5], and Karoli etal[85] have all proven beyond doubt that higher duration of smoking is associated with higher BODE index. The study revealed that there was significant increase in the BODE index in patients with a higher duration of smoking. The difference was not statistically significant among the control group and those in the mild COPD group. This probably means that the disease could still be reversed with the cessation of smoking.

A multiple component staging system combining FEV_1, 6-min walking distance, dyspnea scored with the MMRC scale, and PaO_2 was reported to better describe health-care resources utilization among COPD patients in different geographic areas when compared to international COPD classifications (ATS, British Thoracic Society, and GOLD)[86]. The BODE index was also reported to be a much better predictor of the severity in COPD acute exacerbations than FEV_1[2]. Our findings of the usefulness of the BODE index in predicting hospitalization for COPD are also supported by the findings of a prospective study[29] of risk factors of hospital readmissions for COPD exacerbation. In that study, a strong association between the usual physical activity and reduced risk of COPD readmission was demonstrated. Moreover, the association did not change when adjusted for FEV_1 or nutritional status. These results are in agreement with the increased risk of COPD hospital admission associated with a limited 6-min walking test reported by another group of investigators[23]. Therefore, it may be speculated that the superior value of the BODE index compared to FEV_1 in predicting hospital admissions for COPD that we have observed, is accounted for by the evaluation of physical performance status among the individual components of the BODE scoring system.

Admission to the hospital and heavy use of health-care resources is a common feature of COPD. A clinical implication of the present study is that the

BODE scoring system may prove to be helpful in health-care resource allocation and in guiding therapy for individual patients in the future. This multistage scoring system, which incorporates variables that can be evaluated easily in any office setting, should not be difficult or costly to implement routinely. As the BODE index can provide useful prognostic information of survival and hospitalization, the findings of the present study are in support of the utility of the BODE index as an assessment tool for COPD patients.

To our knowledge, this is the first study to show that the BODE staging system predicts the severity of systemic involvement in patients with COPD. The parameters that we assessed to this regard were the body mass index, hemoglobin and albumin concentration, ECG axis, ejection fraction and pulmonary hypertension in ECHO and systemic inflammation as assessed by the CRP value.

While considering BMI as a criteria for BODE index scoring, significance is only given to whether it is more, or less than 21. In our study we found that the BMI progressively declines with severity among the patients with COPD. Emil etal[4] had described the depletion of free fat mass and thereby a reduction in BMI in patients with COPD. Our finding is further supported by various studies[69, 70] that evaluated the systemic effects of COPD. An imbalance in

the continuously ongoing process of protein degradation and replacement can be hypothesized as a mechanism contributing to this wasting condition.

Polycythemia has frequently been reported in patients with COPD, owing to the increased erythropoietin production induced by chronic hypoxia. However in our study we found that in the group with mild disease according to BODE scores, the mean hemoglobin concentration was lower than the control group. But as severity increases the mean hemoglobin concentration was found to increase. Though the initial decrease was statistically insignificant, it could be attributed to the nutritional deficiencies that occur due to the disease state. More studies are required to prove this.

Burch et al[65] and Caird et al[69] have shown that most of the cases (80%) of severe COPD are associated with right axis deviation. We could replicate this in our study population. In our study 61.7 % of individuals had normal axis, 28.3 % had right axis deviation, 7.5 % LAD and 2.5 % had northwest axis. However in the severe COPD group 86.3 % individuals had right axis and 10.3 % Northwest axis which was significantly higher compared to other groups. This could be attributed to the higher level of deterioration in lung function and pulmonary hypertension in these individuals.

The echocardiography findings in our study were generally in agreement with other studies conducted. However studies have detected only mild reduction in ejection fraction among patients with COPD. In our study the reduction in ejection fraction was very significant especially in the group with severe COPD. This could probably be because of higher incidence of other causes of dilated cardiomyopathy in our group like ischemia, as smoking is a common risk factor. The LV dysfunction in COPD is believed to be due to Bernheim's effect due to paradoxical movement of the interventricular septum in patients with COPD.

Arcasoy et al[87] has demonstrated an incidence of pulmonary hypertension of around 16 % in patients with COPD. Stevens et al[88] showed that the proportion of patients with pulmonary hypertension is higher among patients with severe COPD. Our study revealed a total incidence of 32.5 % of PAH among patients with COPD. The proportion was higher in the severe group with 58.6 % having moderate PAH and 24.1 % having severe PAH. The pulmonary hypertension in patients with COPD occurs due to a variety of factors including pulmonary vasoconstriction due to alveolar hypoxia, acidemia and hypercarbia; compression of pulmonary vessels due to increased lung volume; loss of small

vessels due to lung destruction, and increased blood viscosity and cardiac output due to polycythemia secondary to hypoxia.

Li et al[80] have reported direct effects of TNF α and demonstrated time-dependent and concentration-dependent reductions in total protein content in patients with COPD. Wouters et al[81] also demonstrated hypoalbuminemia in patients with COPD. In our study we found significant reduction in serum albumin concentrations with increase in severity of COPD as assessed by the BODE score.

Among the markers of systemic inflammation, we concentrated on C reactive protein since it has been shown to upregulate the production of proinflammatory cytokines and tissue factors by monocytes, increase the uptake of LDL by macrophages and directly induce expression of adhesion molecules by the human endothelial cells. Additionally CRP may deposit directly into the arterial wall during atherogenesis, interacting with other inflammatory mediators to create foam cells, which serve as building blocks to atherosclerotic plaques. Cirillo et al [90] showed an increasing CRP value with worsening airflow obstruction. Our study has shown that moderate and severe, but not mild COPD is associated with significant levels of low grade systemic inflammation. Study done by Sin et al[89], also revealed similar findings.

LIMITATIONS OF THE STUDY

1. We would like to acknowledge that a relatively small number of patients were evaluated and that the number of patients required to detect a significant difference in the predictive power of the BODE index and FEV_1 were not been prospectively determined.
2. The study is a hospital based study and may not be representative of the general population.
3. Caution is required while using the results in populations outside India because there have been no systematic comparisons of the regional manifestations of COPD.
4. Only males were inducted into the study. Hence the results of the study cannot be used in female patients with COPD.
5. As a cross sectional study, the present analysis is limited in its ability to elucidate, whether improving the BODE index reverses the various parameters analyzed.
6. Alternate causes and medication effects influencing the parameters analyzed should also be considered.

CONCLUSIONS AND SUMMARY

1. BODE index can be used as a reliable index to assess the severity of chronic obstructive pulmonary disease.
2. BODE index is directly correlated with the duration and intensity of smoking.
3. BODE index predicts hospitalization due to causes related to COPD.
4. Polycythemia is associated with more severe disease.
5. Cardiac effects of the disease increases with the severity of disease as assessed by BODE index.
6. BODE index directly correlates with nutritional derangement in patients with COPD as evidenced by the changes in BMI and serum albumin.
7. Intensity of systemic inflammation increases with increase in the severity of disease.

Thus our study concludes that BODE index is reliable method to predict hopitalisation and the severity of systemic involvement in patients with COPD. Since the assessment of BODE index requires only a spirometer, which is relatively inexpensive and can easily be made available, this index could be of great practical value in a primary health care setup to

identify individuals who are at need for further evaluation in a higher center. Thus the BODE index can be used for judicious referral of patients with COPD thereby preventing the wastage of the limited resources available.

SCOPE FOR FUTURE STUDIES

The study conducted in our population has many significant observations and potential implications. Our study concludes that BODE index is reliable method to predict hospitalization and the severity of systemic involvement in patients with COPD. Future studies are needed to assess whether it can be used as a reliable index to monitor the progress of disease. Studies are also needed to assess whether reduction in BODE index improves the disease status. The incidental finding whether hemoglobin concentration decreases initially in patients with COPD could also be subjected to further research.

Future research should also aim at finding the intervention measures which have the greatest impact on BODE index and thereby the severity of the disease. We do not know whether it will be a useful indicator of the outcome in clinical trials, the degree of utilization of health care resources, or the clinical response to therapy. More studies are needed in this regard.

To summarize, the BODE scoring system is reliable index to predict hospitalizations and the severity of systemic involvement in patients with COPD. Besides its excellent predictive power with regard to outcome, the BODE index is simple to calculate and requires no special equipment. This makes it a practical tool of potentially widespread applicability.

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PROFORMA

Name: age: sex: serial no:

Occupation: address:

Symptoms:

Smoker : Y/N

Cough : Y/N

Sputum – nil / scanty / moderate / copious

Breathlessness – nil / exertional / orthopnea / PND

MMRC scale : 0 1 2 3 4

Seasonal variation : Y/N

Nocturnal symptoms: Y/N

Exclusion history:

H/o Unrelated life threatening major illness (If yes specify):

H/o Spirometry proved bronchial asthma :

H/o Myocardial infarction in the past 4 months: Y/N

H/o unstable angina : Y/N

H/o congestive heart failure : Y/N

H/o inability to walk : Y/N

End points:

Number of hospital admission in the past 2 yrs due to causes directly related to COPD:

Examination:

Body wt → Height →

BMI {Wt (kg)/ [Ht(ms)]^2 }→

Cyanosis: clubbing: edema:

JVP:

PR: BP: RR:

Respiratory system:

AP diameter : Transverse diameter:

Rhonchi : Y/N Crepitations : Y/N

Other systems:

Investigations:

Hb – **TC** **DC**

ECG → QRS AXIS – P pulmonale →

Echo → EF – PAH – RV diameter –

6 min walk test → >350 ms / 250 – 349 / 150 – 249 / <149

FEV1 → >/= 65 / 50 – 64 / 36 – 49 / < /= 35

FEV1/FVC →

Post bronchodialator FEV1→

CRP→

LFT **total prot :** **albumin :**

Estimated BODE score → score

- FEV1 →
- Distance walked in 6 mins →
- MMRC dyspnea scale →
- BMI →

---

* **Total BODE score →**

MMRC dyspnea scale

Grade 0 – no dyspnea / only on severe exertion

Grade 1 – dyspnea on hurrying / walking up a hill

Grade 2 – walks slower than normal at level/ pause while walking on level ground

Grade 3 – stops for breath after walking 100 yards/few mins on level ground

Grade 4 – too breathless to leave the house/ dyspnea on dressing

BODE INDEX:

BODE score	0	1	2	3
FEV1	>/= 65 %	50 – 64%	36 – 49%	< /= 35%
6 min walk test	>350 ms	250 – 349ms	150 – 249 ms	<149 ms
Dyspnea scale	0 – 1	2	3	4
BMI	> 21 kg/m^2	<21 kg/m^2		

Mild COPD → 0 – 2

Moderate COPD → 3 – 5

Severe COPD → >/= 6

INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE,
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K.Dis.No.16328 P & D3/Ethies/Dean/GGH/08 Dated: 2/9/2008

Title of the work	:	**A study on BODE index as a predictor of severity and systemic involvement in patients with chronic obstructive pulmonary disease**
Principal Investigator	:	**Dr Sojan George K**
Department	:	**Institute of Internal Medicine, MMC, Chennai 3**

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10th sep 2008 at 2 P.M in GI GI H , Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH,CHENNAI

DEAN
GGH &MMC, CHENNAI

RKM.5.6(2)

ABBREVIATIONS

COPD → Chronic obstructive pulmonary disease

FEV1 → forced expiratory volume in one second

BODE → body-mass index (B), airflow obstruction (O), dyspnea(D), and exercise capacity (E)

GOLD → Global initiative for obstructive lung diseases

ATS → American Thoracic Society

ERS → European Respiratory Society

RV → Residual Volume

FRC → Forced Respiratory Capacity

TV → Tidal Volume

α 1 AT→ Alpha 1 antitrypsin

HNE → Neutrophil elastase

BCM → Body cell mass

FFM → Fat free mass

BMI → Body mass index

IFN → Interferon

CRP → C reactive Protein